Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 62; Numer/Number 2/2011
ISSN 0423–104X

Diabetic pulmonary microangiopathy — fact or fiction?

Cukrzycowa mikroangiopatia płucna — fakt czy mit?

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Abstract

Elevated levels of serum glucose have deleterious effects on the walls of blood vessels, leading to microangiopathy. Such a destructive process involves also pulmonary circulation, where it is referred to as diabetic pulmonary microangiopathy. This hypothesis has been confirmed in histopathologic examinations of pulmonary parenchyma, as well as in pulmonary function tests. However, so far there have been no clinical implications of these findings.

Another phenomenon requiring further discussion involves diabetics with clinically silent respiratory dysfunction. That may result from significant vascular and ventilation reserves that compensate for partial loss of pulmonary parenchyma in the course of diabetes.

In this review, we present an overview of the available publications on pulmonary microangiopathy and its influence on the functioning of the respiratory system. **(Pol J Endocrinol 2011; 62 (2): 171–175)**

Key words: *diabetes mellitus, lung microangiopathy, pulmonary function tests, lung diffusing capacity for carbon monoxide*

Streszczenie

Ponadfizjologiczne stężenia glukozy we krwi wpływają destrukcyjnie na ściany naczyń krwionośnych, prowadząc do rozwoju mikroangiopatii naczyniowej. Uszkodzeniu ulegają również naczynia płucne, wywołując cukrzycową mikroangiopatię płucną. Fakt ten znajduje potwierdzenie w badaniach histopatologicznych miąższu płuc oraz w badaniach czynnościowych układu oddechowego. Jednakże wciąż nie ma implikacji klinicznych dla wykorzystania tej wiedzy w codziennej praktyce klinicznej dla tej grupy chorych. Wiązać się to może z olbrzymią rezerwą naczyniową i pojemnościową płuc, która kompensuje częściową utratą miąższu płucnego w przebiegu cukrzycy. W pracy przedstawiono przegląd dostępnego piśmiennictwa dotyczącego mikroangiopatii płucnej i jej wpływu na stan czynnościowy układu oddechowego. **(Endokrynol Pol 2011; 62 (2): 171–175)**

Słowa kluczowe: *cukrzyca, mikroangiopatia płucna, testy czynnościowe płuc, pojemność dyfuzyjna płuc dla tlenku węgla*

Introduction

Diabetes mellitus, generally considered a 'civilisation' disease, is a metabolic disorder characterised by chronic hyperglycaemia and impaired metabolism of carbohydrates, proteins and lipids. Glucose metabolism disorders result from impaired insulin secretion (insulin deficiency), insulin resistance or the coexistence of both mechanisms. Diabetes is a significant social problem, affecting more than 220 million people worldwide [1]. Two major types of diabetes have been identified (type 1, type 2) as well as several other types that are diagnosed less often. Type 2 diabetes is the commonest form of the disease, accounting for about 90% of diabetics [1]. The number of newly diagnosed cases correlates with age. Obesity is another factor that favours an abnormal carbohydrates metabolism, leading to impaired fasting glucose and/or impaired glucose tolerance (the so-called 'pre-diabetes').

Elevated levels of blood glucose have a destructive influence on the walls of blood vessels, leading to microangiopathy, which affects the structure and function of vessel walls. The process involves the destruction of arterioles (precapillar vessels), venules (postcapillar vessels) as well as networks of capillaries of numerous organs. Diabetic microangiopathy encompasses retinopathy, nephropathy and peripheral neuropathy. These complications frequently result in loss of vision and chronic renal insufficiency [2]. As a result of microangiopathic complications, diabetics are also earlier and more often affected by coronary heart disease, stroke and atherosclerosis [3].

Molecular aspects of diabetic microangiopathy

Inflammation and oxidative stress caused by chronic hyperglycaemia play significant roles in the develop-

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ment of chronic diabetes complications. Sustained hyperglycaemia induces disadvantageous biochemical and metabolic changes in all body tissues. In the vascular endothelium, non-enzymatic glycation of proteins and autoxidation of glucose lead to the production of reactive oxygen species — superoxide anions (O_2^-) (oxidative stress) [4]. They provoke molecular changes in cells, including the activation of proinflammatory cytokines: IL-1β (interleukin), IL-6, IL-8, TNF-α (tumour necrosis factor α), as well as PKC (protein kinase C) [5]. Oxidative stress induces functional changes in the epithelium. Stimulated epithelium secretes vascular endothelial growth factor (VEGF), which is responsible for neovascularisation typical of diabetes [6]. The procoagulatory activity of the epithelium is also elevated. Together with abnormal regulation of vessels' tonus, it leads to impairment of blood flow in capillaries [7]. Continuously activated proinflammatory factors lead to the formation and consolidation of 'metabolic memory' [8].

Blood flow in microcirculation is additionally disturbed by polymorphonuclear neutrophils (PMN). These are considered to play a crucial role in the development of diabetic microangiopathy by the phenomenon of leucoembolisms. Due to hyperglycaemia, they lose their natural ability to change their shape, which may cause the blocking of small vessels (with a diameter below 10 μm) [9].

Chronic inflammation associated with diabetic abnormalities causes impairment of the vascular bed in several organs, including the lungs. The intensity of inflammatory processes is reflected by elevated levels of biochemical markers of inflammation, such as CRP (C-Reactive Protein) and fibrinogen [10, 11]. In numerous studies, a correlation has been found between increased levels of CRP, fibrinogen and the development of microangiopathic complications in patients suffering from diabetes type 1 or type 2 [12–14].

Histopathologic characteristics of pulmonary microangiopathy

Microangiopathies, particularly retinopathy, nephropathy and neuropathy, are well-known complications of diabetes. Less well-known, but still significant, is the influence of abnormal glucose metabolism on the functioning of the respiratory system (pulmonary microangiopathy). Generally accessible databases lack studies concerning the influence of diabetes on the lungs. To a certain degree, that results from complicated techniques of intravital material collection. Samples collected routinely by transbronchial biopsy are unreliable in an analysis of diabetic abnormalities in pulmonary parenchyma and circulation [15]. Experimental studies conducted on animals, as well as autopsies of diabetics with no concomitant pulmonary conditions (i.e. they died from cardiovascular causes), have revealed that lungs, with their vast, dense circulation system, are subject to pathologic changes related to hyperglycaemia [16–18]. Two types of histological changes have been described in the lungs [19, 20]:

— thickening of walls of pulmonary alveoli caused by increased amounts of collagen and elastin; thickening of a basal membrane of alveoli, which leads to a decrease in pulmonary parenchyma elasticity;
— thickening of a basal membrane of capillaries (fibroblast proliferation) and endothelium; increased density of pulmonary microvessels.

A correlation has been found between the time from the onset of diabetes and the grade of renal pathology (diabetic nephropathy). Such a link has not however been confirmed in relation to pulmonary changes. This may be partly explained by different blood pressure in different organs [20]. Diabetes leads to impairment of the alveolar-capillary membrane. Its consequences include lengthening of the distance and time of gas exchange between interior of alveoli and erythrocytes in pulmonary capillaries. Thickening of the barrier results in a decrease in oxygen saturation in erythrocytes [21].

Pulmonary function tests in diabetics

Associations between lung function deterioration and diabetes have been widely discussed for many years. Non-invasive methods of diagnosing pulmonary microangiopathy include spirometry and measurement of lung diffusing capacity for carbon monoxide (DLCO) [22]. However, it seems that single spirometry is not sensitive enough to make a precise diagnosis [23]. Better results can be achieved in consecutive measurements of ventilation parameters over longer periods of time. In some studies, in long-term observations a decrease in FEV_1 (forced expiratory volume in one second) and FVC (forced vital capacity) values have been found in diabetics. Davis et al. [24] analysed the influence of glycaemia control on the values of FEV_1 and FVC. In a group of 125 non-smoking patients suffering from diabetes type 2, spirometry was performed at the beginning of the study and again after seven years of observation. A significant decline of FEV_1 was revealed in the diabetes group compared to healthy, non-smoking controls. In the group of diabetes patients, annual FEV_1 decline was 71 ml and in the control group it was 25–30 ml. What is more, a decline of 10% in FEV_1 was an independent risk factor for death. Additionally, the study revealed correlation between FVC decline and an increase of HbA_1c (glycated haemoglobin) fraction. Every increase of 1% in HbA_1c level was associated with a FVC decline of 4% predicted value. These observations have

been confirmed by other studies. The Normative Ageing Study showed that men predisposed to diabetes or with diabetes had lower FEV_1 and FVC in both the period before diabetes development, and after diagnosis, compared to a control group [25]. Similar correlations were found in the prospective ARIC (Atherosclerosis Risk in Communities) study [26]. This was conducted on a population of 1,100 patients with diabetes type 2 of varied severity and treatment applied (smokers and non-smokers). The control group consisted of 10,162 healthy middle-aged subjects. Over a three-year follow-up, a significant decrease of FVC in diabetic patients was observed compared to the control group (64 *v.* 58 ml/year; $p = 0.01$). Recently, Borst [27] presented a meta-analysis of 40 studies on lung function in 3,182 diabetics and 27,080 healthy controls. On the basis of literature review, it was found that diabetes was associated with mild, but still significant, ventilation abnormalities of restrictive pattern.

On the other hand, the literature does not contain reliable studies concerning an application of whole body pletysmography in the evaluation of respiratory function in diabetic patients. It seems that measurements of total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV) and lung resistance (Raw_{tot}) may play crucial roles in the evaluation of the respiratory system in this group. However, available data on this subject is somewhat scarce [28].

Impairment of the alveolar-capillary membrane is an essential part of pulmonary complications of diabetes. As a consequence, DLCO has a practical application in the evaluation of pulmonary involvement [29]. The first study in this field was published in 1976 by Schuyler et al. [30], who revealed a decrease in DLCO in 11 young men with type 1 diabetes. The group consisted of non-smokers with no concomitant respiratory or allergic diseases. At the same time, no changes were found in a control group consisting of healthy men aged 21–28. In contrast, Schernthaner et al. did not confirm diffusion impairment in a similar population of diabetics [30].

Sandler et al. [32] presented data confirming malfunction of the alveolar-capillary membrane in diabetes. In a group of 22 young non-smokers with insulin-dependent diabetes, they found significant DLCO/VA decline (5.25 ± 0.68 *v.* 5.61 ± 0.57 ml/min/mm Hg/L, $p < 0.05$). In the authors' opinion, this was caused by lower blood volume in pulmonary capillaries. Similar results have been obtained in a population of children with insulin-dependent diabetes. Villa et al. [33] evaluated pulmonary function and DLCO in 39 children with type 1 diabetes (age: 10.9 ± 2.6 years, mean time from diabetes onset: 3.6 ± 2.4 years) and in 30 healthy control children (mean age 10.4 ± 3.0 years). No significant differences were found in spirometry (FVC and FEV_1) between the groups. However, in children with poor control of glycaemia (HbA_1c 8.7% ± 0.5%), lower values of DLCO/VA were found compared to healthy controls (DLCO/VA 86.7% ± 12.6% *v.* 102.0% ± 15.7%, $p = 0.013$). Low DLCO in diabetic children directly correlated with metabolic instability.

Additionally Fuso et al. [34] showed a decrease of DLCO in diabetic patients lying supine compared to measurements made when the subjects were sitting. Changes associated with body position were not observed in healthy controls. In contrast, in the general population, DLCO increases in a supine position. The authors' own studies [35] also showed DLCO decline depending on body position. Mean DLCO/VA in diabetics was: 1.58 mmol/min/hPa (91%) while standing, 1.29 mmol/min/hPa while lying supine (73%), and 1.12 mmol/min/hPa (63%) while lying prone. In the control group, mean DLCO/VA values were: 1.38 mmol/min/hPa (73%), 1.44 mmol/min/hPa (77%) and 1.24 mmol/min/hPa (67%) respectively. DLCO/VA (direct and indirect) was significantly lower in diabetics in both supine and prone positions ($p < 0.05$ and $p < 0.01$). Moreover diabetic patients had higher levels of CRP and HbA_{1c} compared to the control group ($p < 0.01$).

It seems that the DLCO decline in subjects lying down results from structural abnormalities of pulmonary capillaries (decrease of vessels' lumen) and thickening of alveoli walls. This mechanism is associated with longer distance between interior of alveolus and capillary that has to be covered by diffusing gases [36]. Changing body position additionally decreases blood volume flowing through capillaries. In contrast, in healthy individuals with no impairment of pulmonary function, changing body position does not have any influence on blood volume in pulmonary capillaries. In this population, DLCO values are similar irrespective of body position, or they may be even higher while lying down. This might be due to widening of the pulmonary vascular bed while lying down.

Lungs are filled with the largest network of capillaries in the human body. Their surface is estimated to exceed 140 m^2. Physiologically, a part of pulmonary microcirculation is inactive. Closed vessels are gradually being recruited in case of higher demand for oxygen, e.g. during physical exercise. Normally, this mechanism also leads to an increase of DLCO. Such adaptation has not been observed in patients with type 1 diabetes. What is more, DLCO decline is observed both before and after physical exercise [37].

On the other hand, it is known that diabetes, particularly type 2, is associated with obesity. Obesity increases blood volume and cardiac output, which in turn leads to a DLCO increase [38]. This compensation makes DLCO decline a gradual and long-lasting process in obese diabetics.

Diabetes affects the strength and endurance of respiratory muscles, particularly the diaphragm [39]. It also has a deleterious effect on collagen structure in pulmonary parenchyma and cartilages of chest wall [40]. All these changes limit chest mobility [41].

Another important aspect of long-term diabetes complications is involvement of autonomic nervous system in almost every organ, including the lungs. It has been shown that dysfunction of cholinergic system [42] and adrenergic denervation [43] are significant parts of the clinical picture of diabetic neuropathy. Pathologic changes in respiratory muscles, together with damage to chest cartilages and malfunction of the vegetative system, deteriorate lung function in diabetic patients.

Diabetes therapy with inhaled insulin — pros and cons

In recent years, several attempts have been made to introduce inhaled insulin (Exubera® Inhalation Powder, Technosphere® Insulin) into clinical practice [44, 45]. Clinical trials have confirmed the hypoglycaemic activity of this form of insulin in both type 1 and type 2 diabetes [46, 47]. Nevertheless, application of this form of insulin has been found to have many limitations. Due to decreased absorption from pulmonary alveoli, it is contraindicated in current smokers and patients who ceased to smoke in the previous six months [48]. Its use is not indicated in patients with asthma or COPD [49]. Moreover, several publications have outlined a fall in DLCO during therapy with inhaled insulin [50, 51]. Some authors have also reported a loss of glycaemia control with an increase in the level of anti-insulin antibodies [50, 52]. That is why further studies are necessary to assess the impact of inhaled insulin on pulmonary function.

Conclusions

Pulmonary involvement in the course of diabetes has been investigated for many years. Impairment of lung function is a fact confirmed by histopathology of pulmonary parenchyma as well as function tests. Despite the large number of studies, they still do not have any implications that could be used in everyday practice. So far, no easily-accessible and acceptable methods have been introduced for early detection and monitoring of pulmonary microangiopathy. This fact may be associated with the huge vascular and capacitive reserve that compensates for partial loss of pulmonary parenchyma in the course of diabetes, and makes the complication clinically silent.

Studies on diabetes-related vascular abnormalities may be enhanced by the attempts to introduce inhaled insulin into routine therapy. In the future, such studies could bring significant cognitive, clinical, prophylactic and financial benefits. As a consequence, they may lead to amelioration of complex care for patients suffering from type 1 or type 2 diabetes.

This is why regularly performing basic functional tests of the respiratory system (spirometry, DLCO) in certified centres should be recommended to all patients in order to diagnose early diabetic pulmonary microangiopathy.

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